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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,649	03/30/2001	Edward Soh Smith	RPA1006	8561

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	11

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,649	SMITH ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed November 12, 2002. Currently, claims 1-52 are pending.

Election/Restrictions

2. The restriction made April 24, 2002 has been withdrawn in view of applicant's arguments and traversal filed November 12, 2002. Claims 1-52 have been fully examined in the action below.

Priority

3. This application claims priority to provisional application 60/198,336, filed April 18, 2000.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 8-13, 20-29, 36-41, 48-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reverse transcribing an RNA using a mutant DNA polymerase characterized in that in its native form said DNA polymerase comprises SEQ ID NO: 3, and at position 4 of said amino acid sequence the amino cid is other than E,A,G or P, does not reasonably provide enablement for any mutant polymerase of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn methods for reverse transcribing an RNA using a mutant DNA polymerase wherein the DNA polymerase is characterized in that "in its native form the DNA polymerase comprises amino acid sequence of SEQ ID NO: 1." SEQ ID NO: 1 is LeuXaaXaaXaaXaaXaaXaaXaaXaaXaaGlu where Xaa at positions 2, 2, 5, 6, 7, 8, 9, 10 are any amino acid, Xaa at position 4 is not Glu, A, G or P.

The specification teaches six more specific genus within the very broad genus of SEQ ID NO: 1. These genus are identified by SEQ ID NO: 2-7. The specification, in

Table 1, provides an alignment of "the critical motif" of DNA polymerases. The Table highlights position 4. The specification teaches that each of the mutant polymerases had been previously disclosed. The "critical motif identifies a particular functional fegion within the polymerase domain of the enzyme, and identifies an amino acid within the motif that is critical to the function" (page 12, lines 35-38). The specification asserts that the structural relatedness of DNA polymerases and the presence of conserved functional domains is well known. The specification explains that "additional substitution mutation in position 3 of the critical motifs identified as SEQ ID NO: 1-7 may provide additional benefits" (page 14, lines 14-16). The specification provides a single example of the effects on Mg-activated reverse transcription efficiency of each possible mutation at this site in one widely used thermostable DNA polymerase, Thermus thermophilus DNA polymerase. In Example 1, a "series of 19 mutant DNA polymerases were constructed from "native" Termus thermophilus (Tth) DNA polymerase representing all possible mutations in the critical amino acid (page 18). The results of the reaction efficiencies are provided for each of the possible mutations at position 4 (page 24).

As claimed, the independent claim, namely Claims 1, 13, 29, 44, encompasses any DNA polymerase which minimally contains a Leu amino acid separated by 10 variable positions and Glu at position 11. The specification teaches a single example of a very defined structure with a single variable position, namely position 4. The claims are drawn much broader to read on a large genus of sequences which have not been defined by the specification with respect to their reaction efficiencies. The specification teaches that position 681 is the critical amino acid for Taq polymerase, however the

polymerase taught in the specification, also contains an F667Y mutation and a G46D mutation. The specification does not teach how these extra mutations would function in reverse transcription efficiencies. As seen in the alignment provided in Table 1, the identified critical motif contains many conserved positions among several species, however, not complete conservation between all species. It is unpredictable which of the additional positions within the "critical motif" would affect the reverse transcription properties of the polymerase. The specification has demonstrated on specific example, namely SEQ ID NO: 3 with each of the variations between the possible mutants. Given the teachings from this example, it is unpredictable how additional mutations or variations within SEQ ID NO: 3 will affect the reaction efficiencies of alternative polymerases. In the broadest claim, SEQ ID NO: 1 identifies only 3 of 11 positions within the polymerase. This very broad definition of structure does not provide guidance to the skilled artisan how to use the entire scope of the claims. Absent undue trial and error experimentation, to determine whether each of the possible alternatives have the DNA polymerase activity, the skilled artisan would be unable to use the invention as broadly as claimed. There are 20 possible alternatives for each of the 8 undefined positions within SEQ ID NO: 1. Given all of the possible permutations encompassed within the claim, the claim encompasses 25,600,000,000 different amino acid sequences. While one could conduct additional experimentation to determine whether, e.g. each of these permutations might have DNA polymerase activity, the outcome of such research cannot be predicted and such further research and experimentation are both unpredictable and undue.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 5-7, 17-19, 33-35, 45-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 5-7, 17-19, 33-35, 45-47 are indefinite over the recitation "is mutated in comparison to said native sequence to an amino acid other than E, A, G, or P" within Claim 1 because each of the sequences of the claims 5-7, 17-19, 33-35, 45-47 do not contain an E, A, G or P at position 4. SE QID NO: 5 contains a R; SEQ ID NO: 6 contains a R and SEQ ID NO: 7 contains an N. Therefore it is unclear whether the claim requires a further mutation from the native sequence or whether the claim may simply not have an E, A, G or P.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-10, 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Gelfand et al (EP 0 902 035 A2, March 17, 1999).

Gelfand et al. (herein referred to as Gelfand) teaches thermostable DNA polymerases. Gelfand teaches SEQ ID NO: 2, 3, 4, 5, 6, 7, namely SEQ ID NO: 2, 3, 4, 5, 6, 7, respectively of the instant application. Gelfand teaches that the "DNA synthesis reaction" refers to methods of producing copies of DNA including but not limited to PCR, strand displacement amplification, transcription mediated amplification, primer extension and reverse transcription (page 5). Gelfand exemplifies using the enzymes of the invention to efficiently incorporate nucleotides labeled with fluorescein family dye by means of a primer extension competitions assay (col. 10). Gelfand also teaches that the mutant polymerases may be used in sequencing methods. Gelfand teaches the method of DNA labeling by providing a thermostable DNA polymerase, providing a nucleotide labeled and performing a DNA synthesis reaction. The thermostable DNA polymerases of the invention are more suitable and desirable for use in processes such as DNA sequencing and in vitro synthesis of labeled products than prior art polymerases. Therefore, since Gelfand teaches every limitation of the claimed invention, Gelfand anticipates the instant claims.

7. Claims 1-10, 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Gelfand et al (US Pat. 6,346,379, filed September 3, 1998).

Gelfand et al. (herein referred to as Gelfand) teaches thermostable DNA polymerases. Gelfand teaches SEQ ID NO: 2, 3, 4, 5, 6, 7, namely SEQ ID NO: 2, 3, 4,

5, 6, 7, respectively of the instant application. Gelfand teaches that the "DNA synthesis reaction" refers to methods of producing copies of DNA including but not limited to PCR, strand displacement amplification, transcription mediated amplification, primer extension and reverse transcription (col. 7, lines 25-30). Gelfand exemplifies using the enzymes of the invention to efficiently incorporate nucleotides labeled with fluorescein family dye by means of a primer extension competitions assay (col. 10). Gelfand also teaches that the mutant polymerases may be used in sequencing methods. Gelfand teaches the method of DNA labeling by providing a thermostable DNA polymerase, providing a nucleotide labeled and performing a DNA synthesis reaction. The thermostable DNA polymerases of the invention are more suitable and desirable for use in processes such as DNA sequencing and in vitro synthesis of labeled products than prior art polymerases. Therefore, since Gelfand teaches every limitation of the claimed invention, Gelfand anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 11, 13-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gelfand et al (US Pat. 6,346,379, filed September 3, 1998) or Gelfand et al (EP 0

902 035 A2, March 17, 1999) in view of Kawasaki (PCR Protocols, Chapter 3, pages 21-27, 1990).

Each of the Gelfand et al. (herein referred to as Gelfand) references teaches thermostable DNA polymerases. Gelfand teaches SEQ ID NO: 2, 3, 4, 5, 6, 7, namely SEQ ID NO: 2, 3, 4, 5, 6, 7, respectively of the instant application. Gelfand teaches that the "DNA synthesis reaction" refers to methods of producing copies of DNA including but not limited to PCR, strand displacement amplification, transcription mediated amplification, primer extension and reverse transcription (col. 7, lines 25-30). Gelfand exemplifies using the enzymes of the invention to efficiently incorporate nucleotides labeled with fluorescein family dye by means of a primer extension competitions assay (col. 10). Gelfand also teaches that the mutant polymerases may be used in sequencing methods. Gelfand teaches the method of DNA labeling by providing a thermostable DNA polymerase, providing a nucleotide labeled and performing a DNA synthesis reaction. The thermostable DNA polymerases of the invention are more suitable and desirable for use in processes such as DNA sequencing and in vitro synthesis of labeled products than prior art polymerases.

Gelfand does not specifically teach a method of reverse transcription using magnesium, primers and DNA polymerase.

However, Kawasaki teaches amplification of RNA methods which employ PCR buffer comprising magnesium, namely MgCl2. Kawaski teaches that the "magnesium concentration is also critical, so care should be taken that the addition of reagents does not lower the magnesium molarity" (page 26). Kawaski teaches that "the source and

type of reverse transcriptase do not seem to be of critical importance." Kawasaki teaches incubating the reaction mixture at 23 and 42 degrees. Kawaski teaches performing PCR following the reverse transcriptase reaction.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have used the mutant polymerases taught by Gelfand to be useful in reverse transcription assays using the specific method of Kawasaki. The ordinary artisan would have recognized that the method provided by Kawasaki was a standard method of RNA amplification. Since Kawasaki clearly indicates that the source and type of reverse transcriptase does not appear to be critical, the ordinary artisan would have been motivated to have substituted the mutant DNA polymerases of Gelfand because they have demonstrated increased efficiency.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1, 5, 9-10, 12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 23 of U.S. Patent No. 6,346,379.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by or would have been obvious over, the reference claim(s). See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentable distinct from each other because Claim 1, 5, 9-12 of the instant application is generic to all that is recited in Claim 23 of U.S. Patent No. 6,346,379. That is, Claim 23 of 6,346,379 falls entirely within the scope of Claim 1, 5, 9-12, or in other words, Claims 1, 5, 9-12 are anticipated by Claim 23 of 6,346,379. Here, claim 23 of U.S. Patent No. 6,346,379 recites a method of producing labeled DNA which comprises providing a thermostable DNA polymerase of SEQ ID NO: 4, providing a nucleotide labeled with a fluorescein family dye and performing a DNA synthesis reaction. US Pat. 6,346,379 clearly defines the term "DNA synthesis reaction" as referring to methods of producing copies of DNA including but not limited to PCR, strand displacement amplification, transcription mediated amplification, primer extension and reverse transcription (col. 7, lines 25-30). Therefore, the instant claims are generic to the claims of 6,346,379.

10. Claims 11, 13, 17, 20-29, 33, 36-41, 45, 48-52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 23 of U.S. Patent No. 6,346,379 in view of Kawasaki (PCR Protocols, Chapter 3, pages 21-27, 1990).

Although the conflicting claims are not identical, they are not patentable distinct from each other because Claim 1, 5, 9-12 of the instant application is generic to all that is recited in Claim 23 of U.S. Patent No. 6,346,379. That is, Claim 23 of 6,346,379 falls entirely within the scope of Claim 1, 5, 9-12, or in other words, Claims 1, 5, 9-12 are anticipated by Claim 23 of 6,346,379. Here, claim 23 of U.S. Patent No. 6,346,379 recites a method of producing labeled DNA which comprises providing a thermostable DNA polymerase of SEQ ID NO: 4, providing a nucleotide labeled with a fluorescein family dye and performing a DNA synthesis reaction. US Pat. 6,346,379 clearly defines the term "DNA synthesis reaction" as referring to methods of producing copies of DNA including but not limited to PCR, strand displacement amplification, transcription mediated amplification, primer extension and reverse transcription (col. 7, lines 25-30).

Gelfand does not specifically teach a method of reverse transcription using magnesium, primers and DNA polymerase.

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teaches incubating the reaction mixture at 23 and 42 degrees. Kawaski teaches performing PCR following the reverse transcriptase reaction.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have used the mutant polymerases taught by Claim 23 of Gelfand to be useful in reverse transcription assays using the specific method of Kawasaki. The ordinary artisan would have recognized that the method provided by Kawasaki was a standard method of RNA amplification. Since Kawasaki clearly indicates that the source and type of reverse transcriptase does not appear to be critical, the ordinary artisan would have been motivated to have substituted the mutant DNA polymerases of Gelfand because they have demonstrated increased efficiency.

Conclusion

11. No claims allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg
Jeanine Goldberg
January 24, 2003

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600